Depression in Patients with Systemic Sclerosis: A Systematic Review of the Evidence

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ABSTRACT

Objective: To assess the prevalence, course, and predictors of depression in patients with systemic sclerosis (SSc).

Methods: A comprehensive search in November 2006 of MEDLINE®, PsycINFO®, and CINAHL® databases, to identify original research studies published in any language that used a structured interview or validated questionnaire to assess major depressive disorder or clinically significant symptoms of depression in patients with SSc. The search was augmented by hand searching of 26 selected journals through December 2006 and references from identified articles and reviews. Studies were excluded if only an abstract was provided or if depression was not measured by a validated method.

Results: No studies used a structured clinical interview to assess the prevalence of major depressive disorder. The prevalence of clinically significant depressive symptoms was 51-65% based on 2 studies that used a Beck Depression Inventory (BDI) score of ≥ 10 and 46-56% based on 2 studies that used a BDI ≥ 11. These rates and those reported in 4 other studies that used different assessment tools (36-43%) were consistently high compared to other medical patient groups assessed with the same instruments and cutoffs. Methodological issues limited the ability to draw strong conclusions from studies of predictors.

Conclusion: Symptoms of depression are common among patients with SSc. The high rates reported across studies suggest that routine screening is recommended. There is a need for studies that examine depression at different time points from the diagnosis of SSc and that systematically investigate factors associated with high levels of depressive symptoms.

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by abnormal fibrotic processes that can affect multiple organ systems, including the skin, kidneys, lungs, and gastrointestinal tract, as well as cause immune dysfunction and vascular injury. The disease is associated with chronically painful symptoms related to ulcerations, joint contractures, arthritis, gastroesophageal reflux, or Raynaud's phenomenon (1, 2). Although it is a heterogeneous disorder, two common clinical subsets are recognized in terms of skin involvement, limited (skin involvement distal to the elbows and knees) and diffuse (skin involvement proximal to the elbows and knees in addition to the trunk) (3).

High rates of depression are common among patients with chronic medical conditions and are typically several times higher than in the general population (4). Symptoms of depression in patients with chronic illness are associated with emotional suffering, diminished satisfaction with life, impaired functional outcomes, greater healthcare utilization and increased comorbidity and mortality. A growing body of evidence indicates that rather than simply a consequence of medical illness, mood disturbances impact physical health both through physiological pathways and through cognitive, behavioral, and social processes (4). Possible physiological mechanisms include autonomic dysfunction and impaired immune system response. Inflammation and immune system dysfunction are important factors in many different conditions, including cardiovascular disease, osteoporosis, type 2 diabetes, and arthritic conditions, including SSc (5). Behaviorally, symptoms of depression are associated with poor compliance with medical treatment regimens (6), a reduced likelihood of changing harmful behaviors, such as smoking (7), and greater social isolation and fewer attempts to increase social support (8).

Patients with SSc may be at particular risk for depression due to high levels of chronic pain, fatigue, dissatisfaction with their appearance, and overall disability (1, 9, 10). Patients with

SSc commonly report difficulties completing personal care activities, doing household chores, working, or partaking in leisure activities (9). In addition, SSc often results in disfigurement to visible and socially relevant parts of the body (e.g., hands, mouth, face) that can lead to body image dissatisfaction as extensive as among patients with severe burn injuries (11). Among survivors of burn injuries, body image dissatisfaction is an important predictor of symptoms of depression even many years after the burn injury (12, 13).

This systematic review of the literature was carried out to address the following questions: (a) what is the prevalence of depression or clinically significant symptoms of depression among patients with SSc? (b) what is the course of depression or depressive symptoms over time among patients with SSc? (c) what factors predict depression and symptoms of depression? and (d) does depression in patients with SSc improve with treatment?

PATIENTS AND METHODS

Search strategy. The search plan included both electronic and hand searching. The MEDLINE®, CINAHL®, and PsycINFO® databases were searched on November 2, 2006. Search terms are found in Appendix A. The references lists from a recent review of psychological factors in SSc (9) and from all eligible articles were screened to identify any other potentially relevant article titles. In addition, hand searching for eligible articles was done on 26 selected journals (Appendix B) for articles published through December 2006. No searching was done for unpublished articles.

Study selection. Published studies of original research in any language were included if they used a standardized interview or validated questionnaire to assess depression or symptoms of depression in patients diagnosed with SSc. In the case of multiple articles published on the same cohort, only the most relevant article was included. Articles were excluded if they

consisted of case reports or if only a meeting abstract was provided. Studies with mixed patient populations were included only if data on patients with SSc were reported separately.

Two investigators evaluated studies for inclusion. Titles were reviewed, followed by abstracts of selected titles, and, finally, potentially eligible articles. If either investigator selected an article for further consideration during title or abstract review, the article was included in the next stage of review. Discrepancies between reviewers at the article selection stage were resolved by consensus. Author and journal names were not masked since masking does not appear to significantly influence inclusion and exclusion decisions (14).

Data extraction and assessment of methodological quality. Two investigators independently extracted data related to study questions and to methodological quality of the studies reviewed, reconciling differences by consensus. Data extraction forms were developed from consensus among the investigative team regarding the items that were most important for describing the characteristics of each study and summarizing study results. Methodological quality of studies was assessed according to a standardized set of criteria that has been used in previous systematic reviews of observational studies in rheumatic and musculoskeletal disorders (15) and that was modified for the purposes of this review (Appendix C). Studies were rated "yes/no" according to the presence or absence of each criterion in the reports based on the objectives and criteria of this review, which may have been different from the objectives of the primary studies. Items assessed the methodological quality of studies based on the potential for selection bias due to sample size, sampling and response rate, the measurement of symptoms of depression, and, in studies that reported on predictors of depressive symptoms, adjustment for confounding and the quality of statistical methods. Summary quality scores were not created for each study because this approach has been criticized for inconsistent and unsystematic weighting

of different aspects of methodology and over-reliance on the quality of reporting rather than strength of evidence per se (16).

Definition and assessment of depression. For purposes of this review, *depression* was defined as symptoms meeting established clinical threshold criteria for depression as measured by validated questionnaires or standardized psychiatric interviews (17). Questionnaires and rating scales assess symptoms of depression, whereas standardized interviews use Diagnostic and Statistical Manual (DSM) criteria to establish a diagnosis. Although all included studies used instruments validated in at least one patient group, none of the instruments has been validated in patients with SSc. In addition, the manner in which "clinical threshold criteria" is interpreted varied across studies. For example, two studies used a score ≥ 10 on the Beck Depression Inventory (BDI) to report a prevalence of at least "mild depression" (1, 10), whereas two other studies used a cutoff on the BDI of 11 or greater to indicate "depressive mood."

Data analysis. For presentation purposes, 95% confidence intervals for prevalence rates reported by individual studies were generated using the bootstrap method with 1,000 resamples (18). Weighted prevalence rates that combine data from multiple studies were not calculated due to the limited number of studies that used the same assessment tool and threshold. Studies using different assessment instruments and cutoff thresholds were not combined because different methods of assessing prevalence rates for symptoms of depression have been shown to produce systematically different results (17).

RESULTS

Search results. The search process identified 83 unique titles. During the title and abstract reviews, 41 and 21 citations were excluded, respectively, leaving 21 articles for review. Thirteen of these articles were excluded, leaving a total of 8 eligible articles (Figure 1) (1, 2, 10,

19-23). All 8 articles reported data on the prevalence of clinically significant symptoms of depression. Of these articles, 6 also assessed predictors of symptoms of depression (1, 2, 10, 19, 21, 22) (Table 1). One patient cohort was described in two separate articles with only very minor change in the overall sample (1, 11). Results from the larger sample are included in this review (1). Since each article used somewhat different prediction models and predictor variables for depression, however, findings related to predictors from the article that was not included in the review (11) are noted along with the results of the included article (1) in Table 1. There were no studies that used a structured clinical interview to assess for major depressive disorder, no studies that tracked the persistence of depressive symptoms over time or at different stages of the disease, and no treatment studies.

Prevalence of significant symptoms of depression. Eight studies published between 1996 and 2006, which examined a total of 551 patients, reported the prevalence of clinically significant symptoms of depression (Table 1). The studies ranged in size from 31 to 142 patients. Mean age ranged from 46 to 60 years, and the percentage of females from 81% to 100%. Patients in all studies met American College of Rheumatology classification criteria for SSc (24) with the exception of 3 patients in one study (21) and 11 patients in another study (10). Mean disease duration ranged from 6 to 14 years, although some studies defined duration from the onset of Raynaud's phenomenon, other studies from the onset of the first non-Raynaud's manifestation of SSc, and yet others as the time of physician diagnosis of SSc. The percent of patients with diffuse SSc ranged from 24% to 61%. Mean total skin scores ranged from 6 to 17 in the three studies (2, 19, 22) that used a 17-item modified Rodnan skin score (25). Mean total skin score was 10 in one study (21) that used a 10-item modified Rodnan skin score (26). All of the studies reported data on patients from single centers, and all were cross-sectional studies. Three studies

(1, 2, 10) were from the United States, 4 (19-21, 23) were from Europe, and 1 (22) was from Japan. To assess symptoms of depression, 4 studies (1, 10, 19, 22) used the BDI, one (20) used the Montgomery-Asberg Depression Rating Scale (MADRS), one (2) used the Center for Epidemiological Studies Depression Scale (CES-D), one (21) used the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D), and one (23) used the Delusions Symptoms States Inventory / states of Anxiety and Depression scale (DSSI/sAD).

In the 8 studies that assessed symptoms of depression, 36% to 65% of patients had clinically significant symptoms of depression based on the cutoff scores reported. Instruments and threshold criteria, however, varied substantially. Of the 4 studies that used the BDI, 2 from the United States used a score of ≥ 10 to indicate "at least mild symptoms of depression" (1, 10) and reported prevalence estimates of 51% (1) and 65% (10) in 142 and 54 patients, respectively. Two other studies from Italy and Japan used a BDI score ≥ 11 for “depressive mood” and found rates of 56% (N = 111) (19) and 46% (N = 50) (22), respectively. Of the 4 studies that used other instruments, one study from France found that 43% of 42 patients scored at least 16 on the MADRS (20). Another study from the United States reported that 36% of 72 patients scored 16 or greater on the CES-D (26% with CES-D ≥ 19) (2). A study from the United Kingdom reported a rate of 38% (of 49 patients) with a HADS-D ≥ 8 (17% with HADS-D ≥ 11), and a study from Greece found that 42% of 31 patients scored 4 or above on the DSSI/sAD. For instruments where two distinct cutoff scores are commonly used (e.g., HADS-D ≥ 8 and ≥ 11, CES-D ≥ 16 and ≥ 19), both are shown in Table 1.

Predictors of depressive symptoms. Six studies (sample sizes 49 to 142 patients) reported predictors of symptoms of depression (1, 2, 10, 19, 21, 22). Of the 6 studies, 4 used stepwise regression procedures that selected variables for inclusion in the prediction model from

among variables with significant bivariate relationships with depressive symptoms (2, 10, 21, 22); one study used logistic regression to predict high scorers on the BDI by simultaneously entering all bivariate predictors (19); and one study that was described in 2 articles investigated the mediational role of depression in predicting psychosocial function using multiple regression (1) and path analysis techniques (11). No studies used a theoretically-driven model designed explicitly to systematically examine predictors of depressive symptoms across patient demographic (e.g., age, sex), socioeconomic (e.g., education, marital status), health status (e.g., disease duration, severity, organ involvement), and distress related (e.g., body image, fatigue, pain, sleep) variables. In addition, the variables examined across studies differed substantially. Two studies (10, 22) used psychosocial constructs that are closely related to depression (helplessness, resilience, neuroticism) and, as such, would be expected to determine a large proportion of variance prior to entry of other potential demographic, socioeconomic or disease-related predictors. Another study (19) entered many different health and disease-related predictors simultaneously into a regression model, but did not provide data on multicollinearity. As a result of these issues, there was little consistency in results across the studies reviewed and a number of different predictors were identified, including education level, overall disease severity and function, gastrointestinal tract function, pain, and psychological constructs (emotional support, neuroticism, learned helplessness, resilience/coping, and perceived attractiveness).

Methodological quality of studies. Quality characteristics of individual studies are shown in Table 2. In cross-sectional surveys, the generalizability of results depends on the representativeness of samples compared to the larger population of patients, which is a function of both sample size and selection processes. The sample size of studies, however, was generally

small, and only 2 studies included more than 100 patients (1, 19). No studies included patients from more than one center. Four studies documented that they recruited from a consecutive series of patients (10, 20, 21, 23), and four studies reported that at least 70% of eligible patients were successfully recruited (1, 10, 21, 23).

No studies used structured clinical interviews to diagnose major depression. Four studies (1, 2, 10, 21) used self-report questionnaires with standard cutoffs for which comparison samples among medical patients are readily available, including scores of BDI ≥ 10, CES-D ≥ 16 or ≥ 19, and HADS-D ≥ 8 for "possible symptoms" or ≥ 11 for "probable symptoms" of depression. The other studies used instruments that are not used frequently to assess prevalence rates (20, 23) or used non-standard cutoff thresholds for the BDI (19, 22) that made comparison more difficult.

All 6 studies that investigated predictors of symptoms of depression were cross-sectional, and only 3 were rated "yes" for adequate coverage of potential predictors/confounders (2, 21, 22). Only 1 study (reported in 2 articles) met the criteria for high quality statistical methods, including use of theoretically-driven, rather than stepwise, models and adequate sample size for the number of predictors (1, 11). This study, however, provided limited information since its objective was to investigate the role of depressive symptoms as a mediator between pain or body image dissatisfaction and functional outcomes rather than to identify predictors of depressive symptoms per se.

DISCUSSION

The major finding of this systematic review was that, based on validated questionnaires or rating scales, the prevalence of depressive symptoms was consistently high among patients with SSc across studies. Based on a BDI score of 10 or greater, two studies of SSc patients found that 51% and 65% of patients had "at least mild-to-moderate symptoms of depression." Two

other studies that used a more conservative BDI cutoff score of 11 or greater to identify patients with depressive symptoms reported rates of 46% and 56%. These rates are high compared to rates reported in other patient groups when a cutoff score of BDI ≥ 10 was used. For example, studies using a BDI cutoff of 10 or greater found "at least mild-to-moderate symptoms of depression" in 31% of hospitalized post-myocardial infarction (MI) patients (weighted average of 6 studies) (17), 51% of patients hospitalized for congestive heart failure (CHF) (27), and 46% of patients seeking reconstructive services following burn injury (12).

Another study in this review reported that 38% of SSc patients scored 8 or higher on the HADS-D and that 17% scored at least 11. This also appears to be higher than in other patient groups. Studies that used a HADS-D cutoff of ≥ 8 have reported "possible" cases of depression in 16% of post-MI patients (weighted average of 4 studies) (17) and 14% of patients with type I diabetes (28). Studies that have used a HADS-D cutoff of ≥ 11 have found "probable cases" of depression in between 6% and 17% of patients, including 7% in post-MI patients (17), 6% in patients with type I diabetes (28), 9-13% in patients with acute burn injury (29), 7% in patients with chronic obstructive pulmonary disease (COPD) (30), and 11% to 17% in patients with rheumatoid arthritis (31, 32). Another study included in this review reported that 36% of SSc patients scored 16 or greater on the CES-D, which compares to 22% to 42% in patients with COPD (33), outpatients with CHF (34-36), and patients with rheumatoid arthritis (37).

Thus, rates of above-threshold symptoms of depression were consistently as high, or higher, than comparable estimates in other patient groups with acute and chronic disease. The limited number of studies in the review and the use of different measurement instruments and cutoffs did not allow for formal sensitivity analyses to determine whether sample composition (e.g., disease severity) or the region where the study was conducted affected rates. It is of note,

however, that consistently high rates of depressive symptoms were found across a range of settings, including 3 studies from the United States and one each from France, Italy, England, Greece, and Japan.

Important shortcomings in the evidence on prevalence included a lack of studies that reported on the course of depressive symptoms over time or studies that reported rates of significant symptoms of depression at different times from disease onset. Another shortcoming was that, with the exception of only a few patients, the studies reviewed included only patients who met ACR classification criteria for SSc. However, it is well recognized that these criteria lack sensitivity for patients with limited disease (38). Indeed, studies have found that as many as two thirds of patients with limited SSc may not meet the ACR criteria (39). Thus, the prevalence rate of depressive symptoms in this large group of patients remains unknown. Finally, no studies used a structured clinical interview, which is considered the "gold-standard," to assess for major depression among patients with SSc. Because of this, it might be tempting to question whether the high rates of depressive symptoms found across studies of patients with SSc could be related to confounding in measurement of depressive symptoms related to overlap between somatic symptoms of depression and symptoms of SSc. Indeed, symptoms characteristically associated with depression, such as fatigue or changes in sleep patterns, are common medical symptoms that may be experienced by patients with SSc regardless of whether or not depressive symptoms are present. The highest rates of symptoms among studies reviewed were reported on the BDI, and specific concerns have been raised about its validity in medical patients since 7 of 21 items assess somatic symptoms (40, 41). Similarly, modified versions of the CES-D have been suggested for patients with pain disorders and rheumatoid arthritis due to concerns about symptom overlap (42). No studies, however, have actually shown that the measurement of

depressive symptoms with these instruments is biased among medically ill patients. Furthermore, the one study that used the HADS-D, which was designed for medically ill patients and does not include any items about somatic symptoms, found substantially higher rates among SSc patients than have been reported in other studies of medically ill patients.

Results from studies that were reviewed for predictors of depressive symptoms among SSc patients were less clear. Many different potential predictors were assessed across studies, and a relatively long list of predictors was generated. No studies, however, used high-quality, robust analytical paradigms with sufficiently large samples to confidently produce a complete set of predictors, and no studies included symptoms of depression or major depressive episodes that occurred prior to being diagnosed with SSc as predictors. An additional concern involves the limited inclusion in these studies of important aspects of the disease experience, such as pain and body image concerns. Patients with SSc may experience multiple painful symptoms, including those from Raynaud's, digital ulcers, joint contractures, arthritis, and gastroesophageal reflux (9). The majority of patients with SSc face at least mild pain (1, 43) and 10% in one sample described their pain as "distressing" or "horrible" (1). Although several studies have linked pain with general distress or symptoms of depression among SSc patients (1, 43, 44), more work needs to be done in this area. Similarly, only two studies reviewed included body image dissatisfaction (11) or perceived attractiveness (21) as potential predictors of depressive symptoms, and both found a significant relationship. Future research should further examine the relationship of body image dissatisfaction among patients with SSc to depressive symptoms, and interventions that have been shown to be effective in treating or preventing body image dissatisfaction in non-medical populations should be tested among patients with SSc (9).

Although some studies found that SSc severity was a predictor of depressive symptoms (19, 21), other studies did not find links with indices of disease severity or duration (2, 10, 22). It cannot be concluded, however, that such a relationship does not exist since none of the studies reviewed were sufficiently powered or statistically robust enough to claim that the failure to find this relationship is meaningful evidence for its absence. In addition, shortcomings and/or inconsistencies in the measurement of disease severity may have also limited the ability of studies to detect an association with depressive symptoms if indeed there is one. There is currently no well-validated standard method of assessing disease severity in SSc (45), and disease duration is variably defined as the time from the onset of Raynaud's phenomenon, the time from the onset of the first non-Raynaud's symptoms, or the time from diagnosis of SSc. Since Raynaud's phenomenon can antedate the onset of systemic illness by more than a decade (46) and since the diagnosis of SSc can often be delayed by more than 10 years in patients with limited SSc (45), different studies in this review may have included patients at very different stages of disease.

In summary, important findings of this systematic review are that rates of depressive symptoms are high even when compared to other patient groups in which similar methods of assessment were used and that no studies have assessed the impact of the disease course of SSc or treatment on depressive symptoms. The high rates reported in all studies reviewed suggest that routine screening for depression in patients with scleroderma should be recommended. A reasonable method would be to screen initially with one of several short screening tools (1-3 items) that have been validated in primary care settings (47, 48) followed, for patients who screen positive, by screening with a more thorough tool, such as the BDI or the Patient Health Questionnaire (49), and referral to an affiliated mental health professional for patients with

significant symptoms of depression. Future research is needed that addresses limitations identified in this review. The STROBE guidelines for the reporting of observational studies in epidemiology (www.strobe-statement.org) provide a useful outline for designing methodologically stronger studies (50).

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Table 1. Summary of Studies on the Prevalence and Multivariate Correlates of Depression Among Patients with Systemic Sclerosis*

Study	Country	# Subjects	Age in Years (mean ± SD)	% Female	Classification Criteria	% Diffuse†	Disease Duration‡ (mean ± SD)	Total Skin Score§ (mean ± SD)	Assessment of Depressive Symptoms	Cutoffs and Prevalence (95% CI)	Significant Multivariate Predictors of Depressive Symptoms (P < .05)
Beretta 2006 (19)	Italy	111	56 ± 11	92	ACR	24	11 ± 7	6 ± 5	BDI	≥ 11: 56% (47% - 65%)	Patient-rated overall disease severity (VAS)
Legendre 2005 (20)	France	42	58 ± 13	83	ACR‖	43	10 ± 8	NR	MADRS	≥ 16: 43% (33% - 52%)	NA
Nietert 2005 (2)	United States	72	51 ± 12	81	ACR	61	6 ± 8	17 ± 12	CES-D	≥ 16: 36% (27% - 45%) ≥ 19: 26% (17% - 38%)	Years of education; upper GI tract function (GIQLI); functional status (S-HAQ)
Richards 2004 (21)	United Kingdom	49	53 ± 12	86	ACR ¶	33	9 ± 6	10 ± 8	HADS-Dep	≥ 8: 38% (28% - 46%) ≥ 11: 17% (7% - 28%)	Patient-rated overall disease severity (VAS); attractiveness (BAQ-attractiveness)
Matsuura 2003 (22)	Japan	50	60 ± 11	82	ACR	40	14 ± NR	11 ± 9	BDI	≥ 11: 46% (37% - 56%)	Learned helplessness (RAI); Resilience/coping with stress (SOC)
Benrud-Larson 2002 (1, 11)	United States	142	52 ± 14	91	ACR	35	NR	NR	BDI	≥ 10: 51% (42% - 60%)	Physical function (S-HAQ); pain (MPQ); body image dissatisfaction (SWAP)**

Study	Country	# Subjects	Age in Years (mean ± SD)	% Female	Classification Criteria	% Diffuse†	Disease Duration‡ (mean ± SD)	Total Skin Score§ (mean ± SD)	Assessment of Depressive Symptoms	Cutoffs and Prevalence (95% CI)	Significant Multivariate Predictors of Depressive Symptoms (P < .05)
Angelopoulos 2001 (23)	Greece	31	46 ± NR	100	ACR	55	7 ± 5	NR	DSSI/sAD	≥ 4: 42% (32% - 51%)	NA
Roca 1996 (10)	United States	54	NR	85	ACR††	46	NR	NR	BDI	≥ 10: 65% (56% - 74%)	Neuroticism (NEO); disability (HAQ); emotional support (1 item from PAIS)

* ACR = American College of Rheumatology; BAQ-attractiveness = Attractiveness subscale of the Body Attitudes Questionnaire; BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies Depression Scale; DSSI/sAD = Delusions Symptoms States Inventory / states of Anxiety and Depression; GIQLI = Gastrointestinal Quality of Life Index; HADS-Dep = Depression subscale of the Hospital Anxiety and Depression Scale; HAQ = Health Assessment Questionnaire; MADRS = Montgomery-Asberg Depression Rating Scale; MPQ = McGill Pain Questionnaire; NA = Not analyzed; NEO = Neuroticism-Extraversion-Openness Personality Inventory; NR = Not reported; PAIS = Psychosocial Adjustment to Illness Scale; RAI = Rheumatology Attitude Index; S-HAQ = Scleroderma Health Assessment Questionnaire; SOC = Sense of Coherence Scale; VAS = Visual analog scale; 95% CI = 95% confidence interval.

† Defined according to Leroy et al. (3) except Nietert et al., Angelopoulos et al., and Roca et al., which did not specify the definition used.

‡ Defined as time since initial diagnosis of systemic sclerosis except Beretta et al. (time since first systemic sclerosis symptoms) and Nietert et al. (time since first non-Raynaud's manifestations).

§ Defined as modified total skin score (mTSS) (17 body parts, score range 0-51) (25) except Richards et al., which used an earlier version of the mTSS (10 body parts, score range 0-30) (26).

‖ Patients admitted for recent organ involvement were excluded.

¶ 3 patients did not meet ACR criteria. All had Raynaud's phenomenon; two had sclerodactyly, abnormal nailfold microscopy, and esophageal dysmotility; and the third had sclerodactyly and a polymyositis overlap syndrome.

** Body image dissatisfaction was investigated in the same cohort in Benrud-Larson et al., 2003 (11).

†† 11 patients did not meet ACR criteria. All 11 had features of CREST syndrome.

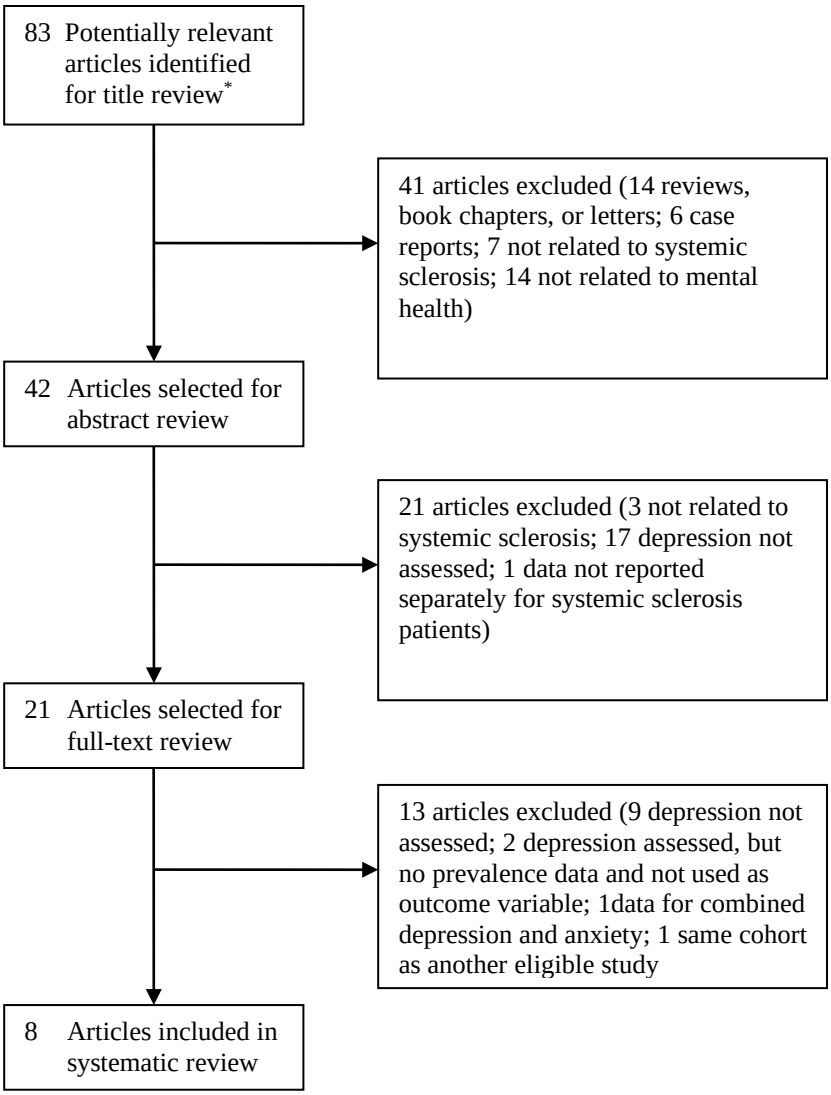
Table 2. Summary of Methodological Quality Characteristics of Studies Reviewed[*]

	Beretta 2006 (19)	Legendre 2005 (20)	Nietert 2005 (2)	Richards 2004 (21)	Matsuura 2003 (22)	Benrud-Larson 2002 (1, 11)	Angelopoulos 2001 (23)	Roca 1996 (10)
Sample Selection and Size								
(1) Systemic sclerosis assessed using ACR criteria	Y	Y	Y	Y	Y	Y	Y	Y
(2) Consecutive series of patients	N	Y	N	Y	N	N	Y	Y
(3) Multi-center	N	N	N	N	N	N	N	N
(4) Selection at uniform point in disease process	N	N	N	N	N	N	N	N
(5) Participation rate ≥ 70%	N	N	N	Y	N	Y	Y	Y
(6) Information provided about non-participants	N	N	Y	N	N	N	-----[†]	N
(7) Description of demographic characteristics included age, sex, and at least 1 socioeconomic indicator	N	Y	Y	Y	Y	Y	Y	N
(8) Description of medical characteristics includes disease duration, disease severity, percent diffuse	Y	Y	Y	Y	Y	N	N	N
(9) Sample size ≥ 100	Y	N	N	N	N	Y	N	N
Assessment of Depression or Symptoms of Depression								
(10) Depression assessed by structured diagnostic interview	N	N	N	N	N	N	N	N
(11) If a structured clinical interview was not used, symptoms of depression assessed with questionnaire and cutoff score that facilitate comparisons with other studies and patient	N	N	Y	Y	N	Y	N	Y

groups								
Predictors								
(12) Coverage of potential predictors included (i) age, (ii) sex, (iii) at least 1 socioeconomic indicator (iv) at least 2 of disease duration, disease severity, percent diffuse, and (v) at least 2 of disability, pain, body image, fatigue	N	-----	Y	Y	Y	N	-----	N
(13) Predictor variables measured prior to outcome	N	-----	N	N	N	N	-----	N
(14) Frequencies or means and standard deviations of all predictors provided	Y	-----	Y	Y	N	N	-----	N
(15) High quality statistical techniques used	N	-----	N	N	N	Y	-----	N

* N = No; Y = Yes. Detailed criteria are presented in Appendix C.
† Reported 100% participation.

Figure 1. Search and Selection of Eligible Articles



* Of 83 potentially relevant articles, 46 were found in MEDLINE®, 6 in CINAHL®, and 40 in PsycINFO®.

Appendix A: Literature Search Strategies

Medline
(scleroderma[mh] OR scleroderma[tiab]) AND (depression[mh] OR depression[tiab] OR depressive symptom*[tiab]) NOT (animal[mh] NOT human[mh])

CINAHL
((scleroderma) and ((depression) or (depressive symptom)))

PsychInfo
((scleroderma OR systematic sclerosis) and ((depression) or (depressive symptom)))

Appendix B: Journals Included in Hand Searching

Annals of Behavioral Medicine
Annals of the Rheumatic Diseases
Arthritis Care and Research
Arthritis Research and Therapy
Arthritis and Rheumatism
Best Practice and Research: Clinical Rheumatology
British Journal of Health Psychology
Clinical and Experimental Rheumatology
Clinical Rheumatology
Current Opinion in Rheumatology
General Hospital Psychiatry
Health Psychology
International Journal of Behavioral Medicine
Journal of Behavioral Medicine
Journal of Health Psychology
Journal of Clinical Rheumatology
Journal of Rheumatology
Psychosomatic Medicine
Psychosomatics
Psychotherapy and Psychosomatics
Rheumatic Disease Clinics of North America
Rheumatology
Rheumatology International
Scandinavian Journal of Rheumatology
Scleroderma Care and Research Journal
Seminars in Arthritis and Rheumatism

Appendix C: Criteria for a "Yes" Rating on Items Assessing Methodological Quality

(1) Systemic sclerosis (SSc) assessed with ACR criteria: Patients were assessed with American College of Rheumatology criteria and degree to which patient sample met criteria was provided.

(2) Consecutive series of patients: Patients were recruited from a consecutive series of clinic admissions or appointments.

(3) Multi-center: Patients from two or more centers were included in data.

(4) Selection at uniform point in disease process: All patients were recruited at a defined time from SSc diagnosis or data were provided separately for patients at different lengths of time from disease onset.

(5) Participation rate ≥ 70%: At least 70% of eligible patients were successfully recruited and participated in the study.

(6) Information provided about non-participants: Demographic data was provided for non-participants or the degree of similarity between participants and non-participants was compared.

(7) Description of demographic characteristics included age, sex, and at least 1 socioeconomic indicator: Data included age, sex, and at least 1 socioeconomic indicator (e.g., income, education, work status).

(8) Description of medical characteristics includes disease duration, disease severity, percent diffuse: Data included disease duration (e.g., time since diagnosis, time since first symptoms, time since onset of Raynaud's phenomenon), validated and appropriately used measures of disease severity (e.g., total skin score or Medsger severity scale ratings), and percent of patients with diffuse symptoms.

(9) Sample size ≥ 100: At least 100 patients were included in analyses.

(10) Depression assessed by structured clinical interview: Major depressive disorder was assessed using a structured clinical interview (e.g., the Structured Clinical Interview for DSM [SCID], the Diagnostic Interview Schedule [DIS], or the Composite International Diagnostic Interview [CIDI]).

(11) If a structured clinical interview was not used, symptoms of depression were assessed with a self-report questionnaire or rating scale and using a cutoff score that enables comparison with other studies and patient groups: Study used a assessment tool and cutoff score combination which is commonly used in other studies of depressive symptoms among medical patients (e.g., BDI $\geq$ 10, HADS $\geq$ 8, HADS $\geq$ 11, CES-D $\geq$ 16, CES-D $\geq$ 19).

(12) Coverage of potential predictors included (i) age, (ii) sex, (iii) at least 1 socioeconomic indicator (iv) at least 2 of disease duration, disease severity, percent diffuse, and (v) at least 2 of disability, pain, body image, fatigue: Predictors eligible for inclusion in multivariate models predicting depressive symptoms included criteria (i)-(v).

(13) Predictor variables measured prior to outcome: Predictor variables were measured at an assessment point prior to the measurement of symptoms of depression.

(15) Frequencies of means and standard deviations of all predictors provided: Frequencies or means and standard deviations of all predictor variables considered for inclusion in multivariate models were provided in text or tables.

(16) High quality statistical techniques used: Descriptions of statistical methods adhered to published reporting guidelines (e.g., *How to Report Statistics in Medicine*, Lang and Secic, 1997; *Publication Manual of the American Psychological Association*, 5th edition, 2001), two-tailed significance tests were used, continuous variables were not artificially dichotomized, automated stepwise procedures were not used unless cross-validated (Freedland et al., Statistical Guidelines for *Psychosomatic*

Medicine, 2005;67:167), and sample size was adequate in relation to the numbers of predictors (e.g., 10:1, *Using Multivariate Statistics,* 4th edition, Tabachnik and Fidell, 2001).